IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
(SHERMAN DIVISION)

ROZLYN ACKERMANN, Individually and as Personal Representative of the Estate of MARTIN LINDSEY ACKERMANN, Deceased, Plaintiff,	§	
vs.	§	CASE NO. 4:05cv84
WYETH PHARMACEUTICALS, Defendant.	§	

PLAINTIFF'S RESPONSE AND MEMORANDUM IN OPPOSITION TO WYETH'S MOTION FOR PARTIAL SUMMARY JUDGMENT (FEDERAL PREEMPTION)

Respectfully submitted,

Andy Vickery
VICKERY & WALDNER, LLP
Texas State Bar No. 20571800
One Riverway Drive, Suite 1150
Houston, Texas 77056-1920
Telephone: 713-526-1100
Facsimile: 713-523-5939
Email: andy@justiceseekers.com

Table of Contents

Table of Authorities

Cases **Page(s)**

Statutes **Page(s)**

Other **Page(s)**

Plaintiff responds to the Motion for Partial Summary Judgment filed by Defendant Wyeth Pharmaceuticals, and would show the Court the following:

I. INTRODUCTION

Martin Ackermann's physician prescribed him Effexor January 4, 2002. On January 17, 2002, he committed suicide by shooting himself. Although Wyeth had data in its possession that should have led it to issue a warning regarding increased suicidal thoughts and behavior prior to January 2002, the FDA had not yet conducted a re-analysis of Wyeth's data using its "standard approach" for adverse reactions. As of January 2002, the FDA neither required nor prohibited an added warning of the association between Effexor and suicide. In early 2004, the FDA began to reanalyze the data that Wyeth and other drug manufacturers possessed for years. In March 2004, the FDA requested that Wyeth warn of the association between Effexor and increased suicidality as to both pediatric and adult patients. The warning as to pediatric patients now appears in a "black box," second only to "contraindications" in terms of "strength" of warning. The FDA is still reanalyzing the data with respect to adult patients, but still requires SSRI manufacturers to warn pending its reanlaysis.

This summary judgment evidence paints a "business-as-usual" picture of federal regulation of prescription drugs for the past few decades. Federal regulations set forth minimum safety standards, but expressly give drug manufacturers the power and the duty to "add or strengthen a contraindication, warning, or precaution" about their drugs, at any time, without prior FDA approval. Ironically, on August 22, 2003, while the FDA waited for it to supply its' reanalyzed data, Wyeth did precisely that with respect to pediatric patients. It issued a *sua sponte* label change and "Dear Doctor" letter, alerting the profession with language in the "Precautions" section, to the increased risk of both hostility and suicidality in pediatric patients taking Effexor. The FDA allowed Wyeth's

precaution to stand for seven months until it requested an even stronger warning for all antidepressants in March 2004. Significantly, the FDA did not sue, or threaten to sue, Wyeth for "misbranding" Effexor by issuing the August 2003 warning, and FDA officials have expressly stated that Wyeth's action was permissible.

Wyeth has now filed a motion for partial summary judgment asserting that Plaintiff's "failure to warn" claim is preempted by federal law. Wyeth attempts to twist (i) its own failure to issue an appropriate warning as to adults before the FDA requested it to do so, (ii) the FDA's refusal to require a warning prior to March 2004 and (iii) a blatantly false assertion that the FDA somehow "revoked" its August 2003 warning concerning pediatric patients into a "positive and direct conflict" that justifies preemption of Plaintiff's claims. To grant this motion, the Court must believe that, if Wyeth had attempted to strengthen its' warning under the applicable federal regulations as to adult patients in or before January 2002 – in the same manner that Wyeth did concerning children and adolescents in August 2003 – the FDA would have considered such a warning "false and misleading," and would have instituted and ultimately prevailed in a suit against Wyeth for misbranding the drug.

This is such a preposterous notion that Pfizer (which pioneered the preemption arguments in suits involving its antidepressant drug Zoloft) has lost the argument outright in seven of the nine cases that have addressed the issue, including every case decided upon a full review of the FDA's activities in 2004 and 2005.[1] Judge Steger of this court has specifically rejected Wyeth's argument

[1] Wyeth identifies two court opinions in its motion. While both while be discussed, at this moment it is important to point out Judge Atlas' opinion in *Dusek* was based on a very narrow stipulation that is inapplicable to the facts at bar, and her opinion makes it clear that her opinion would have been different without that stipulation. It is also of interest that, of the "Big Three" SSRI antidepressants, Eli Lilly's Prozac, GlaxoSmithKline's Paxil and Pfizer's Zoloft, neither Eli Lilly nor GSK has even bothered to pursue a preemption argument.

as applied to a suicide in May 2002: "Given the hearings by both Congress and the FDA regarding suicidality, the FDA's PDAC's recent decision to recommend black box warnings regarding suicidality in children and adolescents, and the numerous experts who have concluded that there is a link between SSRIs, like Zoloft, and suicidality, it would be **inconceivable** to this Court to argue that an additional warning regarding suicidality would be false or misleading." *Cartwright v. Pfizer, Inc.,* 369 F.Supp.2d 876, 885-86 (E.D. Tex. 2005)[emphasis added].

II. THE ANALYTICAL FRAMEWORK: WYETH MUST DEMONSTRATE A "DIRECT AND POSITIVE CONFLICT" THAT SHOULD DISPLACE TRADITIONAL STATE REGULATION OF HEALTH AND SAFETY CONCERNS

Wyeth correctly identifies the three situations in which the Supremacy Clause has traditionally preempted state law: (1) express preemption by Congress, (2) "field preemption," and (3) actual conflict preemption. Wyeth's Motion at 18. Although Wyeth asserts that "[o]nly conflict preemption is at issue here," *Id*. at 18, and generally describes the standards that apply to traditional conflict preemption analysis, *Id*. at 18-19, this case presents a slightly different twist because Congress has expressly directed that there should be no preemption of prescription drug cases absent a "direct and positive conflict."

In any analysis of preemption of state law by federal law, "[the] purpose of Congress is the ultimate touchstone." *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485, 116 S.Ct. 2240, 135 L.Ed.2d 700 (1996). For this very reason, Judge Clark's Order of December 9, 2004 in this case required the parties to focus on the "explicit or implicit preemption provisions found within the text" of the FDCA "or the federal regulations" of the FDA. With respect to prescription drugs, Congress has made its purpose crystal clear. Public Law 87-780, which contained the 1962 Amendments to the Food, Drug & Cosmetic Act, contains the following provision:

> EFFECT ON STATE LAWS
>
> Section 202. Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of state law.

Federal Food, Drug, and Cosmetic Act, 76 Stat. 779 (1962).[2] Similarly, the FDA regulations permit a drug maker to "add or strengthen" a warning at any time, without prior FDA approval. 21 C.F.R. § 314.70. The necessity of a "direct and positive conflict" is consistent with the long-standing presumption against federal preemption, which the advocate of preemption may only overcome by demonstrating"clear and manifest" congressional intent to preempt. *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 715 (1985). Furthermore, the presumption against preemption is even stronger where "Congress [has] legislated . . . in a field which the States have traditionally occupied, [involving] the historic police powers of the States." *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947); *Medtronic*, 518 U.S. at 485. In other words, the presumption is "that state and local regulation of health and safety matters can constitutionally coexist with federal regulation" because "the regulation of health and safety matters is primarily, and historically, a matter of local concern." *Hillsborough County*, 471 U.S. at 716, 719.

Of utmost importance to the case at bar is the U.S. Supreme Court's explanation that "a hypothetical or potential conflict is insufficient to warrant the preemption of" a state law, *Rice v.*

---

[2] Given Congress' express non-preemption of state laws regarding prescription drugs except where there is a "direct and positive conflict" with federal law, it is questionable whether the "obstacle-to-accomplishment" prong of the traditional "actual conflict" test even applies in the case at bar. Plaintiff notes that "obstacles" can be overcome, and thus would not seem to constitute a "direct and positive conflict," which sounds only in impossibility. Even if the "obstacle-to-accomplishment" prong did apply, however, Plaintiff's ability to assert her claim could not possibly thwart the "full purpose and objectives of Congress," when the information-gathering and remedial contributions of state tort litigation are an integral part of the overall scheme of federal regulation of prescription drugs. As discussed below, the primary purpose and objective of the FDCA is to protect consumers.

Norman Williams Co., 458 U.S. 654, 659 (1982). As Plaintiff discusses below, even if Wyeth could prove the existence of the conflict it has identified, that "conflict" is purely hypothetical, and does not even approach "direct and positive."

III. FEDERAL REGULATION OF PRESCRIPTION DRUGS

Congress' primary goal in enacting the Food Drug & Cosmetics Act ("FDCA") was "to protect consumers from dangerous products."[3] *U.S. v. Sullivan*, 332 U.S. 689, 696 (1948). At the time the FDCA was enacted, Congress' stated intent was that the FDCA "must not weaken the existing laws, but on the contrary 'it must strengthen and extend that law's protection of the consumer.'" *U.S. v. Dotterweich*, 320 U.S. 277, 282 64 S.Ct. 134, 88 L.Ed. 48 (1943).

A. Prescription Drugs are Approved for Marketing Based on Minimum Showings of Efficacy and Safety

All prescription drugs in this country must be approved by the FDA prior to marketing. To obtain permission to market a new product, a drug company must first submit a "new drug application" ("NDA") for the FDA's review and approval. 21 U.S.C. § 355(a), (b). An NDA must include information about the clinical trials that demonstrate the safety and effectiveness of the product, proposed labeling, and other information. *Id*. § 355(b), (d). Unfortunately, the information pertaining to adverse side effects gleaned during clinical trials is quite limited.[4] This in turn limits

[3] The 1962 Amendments to the FDCA began with a request from President John F. Kennedy that Congress enact legislation "to advance and protect the interests of consumers in the marketing of drugs." Senate Report No. 1744 on Senate Bill 1744, 1962 U.S.C.C.A.N. at 2888. When Congress enacted the 1962 Amendments to the FDCA, it described the amendments as "An Act to protect the public health . . . ." Pub. L. No. 87-781, 1962 U.S.C.C.A.N at 909 (76 Stat. 780).

[4] Pre-approval clinical trials are neither large enough nor long enough to provide all information regarding a drug's safety. *See* "Commentary on 'The Architecture of Government Regulation of Medical Products'" by Robert Temple, M.D., 82 Va. L. Rev. 1877, 1885-1887 (Nov. 1996) ("It is, in fact, relatively unusual for drugs to be rejected on safety grounds." *Id.* 1885). Ex. 1 at 000267; *see also* "Clinical Therapeutics and the Recognition of Drug-Induced Disease" which states: ". . . **Clinical trials are effective tools primarily designed for assessing efficacy and risk-benefit ratio, but in most cases they are neither large enough nor long enough to provide all information of a drug's safety.")** Ex. 2 at 000142. Indeed, according to a 1990 General Accounting Office (GAO)

the FDA's ability to evaluate the warnings proposed by drug manufacturers as part of the drug approval process.

The recent congressional testimony of FDA epidemiologist, Dr. David Graham, graphically illustrates this point. He testified that "in order to demonstrate a safety problem with 95% certainty [the FDA's standard], extremely large studies are often needed. And guess what? Those large studies can't be done." http://www.finance.senate.gov/hearings/testimony/2004test/111804dgtest.pdf, at 5. Ex. 4. Dr. Graham used the following analogy to prove his point:

> Imagine for a moment that you have a pistol with a barrel having 100 chambers. Now, randomly place 95 bullets into those chambers. The gun represents a drug and the bullets represent a serious safety problem. Using CDER' standard, only when you have 95 bullets or more in the gun will you agree that the gun is loaded and a safety problem exists. Let's remove 5 bullets at random. We now have 90 bullets distributed across 100 chambers. Because there is only a 90% chance that a bullet will fire when I pull the trigger, CDER would conclude that the gun is not loaded and that the drug is safe.

Id.

The nature of the system is that drugs are approved based on clinical trials, with the expectation that the labeling will evolve as a drug's performance is judged in the broader marketplace. The sponsoring drug manufacturer drafts and submits a proposed, initial label to the FDA for approval as part of the NDA process. 21 C.F.R. § 314.105. The FDA either approves the label as submitted by the manufacturer, or requests changes in the label; however, the actual drafting is done solely by the drug company. A drug's label must identify safety hazards, including, in descending order of severity, contraindications, warnings, precautions, and adverse reactions. 21 C.F.R. §§ 201.56, 201.57.

---

report, approximately half of the 198 drugs approved by the FDA between 1976 and 1985 were accompanied by the discovery of serious post-approval risks. Ex. 3 at 000152.

B. Drugs Manufacturers have the Power and the Duty to Add to, or Strengthen, Warnings Without Prior FDA Approval, and Without Proof of Causation

The FDA recognizes that a label for a drug is not a static document, but rather a fluid one that evolves over time. This recognition is based on the limited safety information gleaned during the clinical trial process, and because continued research and disclosure, as well as developing information, can bring other safety hazards to light. As the FDA Commissioner has explained, "[t]he Commissioner recognizes that drug labeling does not always contain the most current information and opinion available to physicians about a drug because advances in medical knowledge and practice inevitably precede formal submission of proposed new labeling by the manufacturer and approval by the FDA." 44 Fed. Reg. at 37435. A drug's label is ever-changing as more information is learned about the drug once it is marketed.[5]

Because the formal labeling always lags behind the current state of knowledge – and because the knowledge and available resources of drug manufacturers are almost always superior to that of the FDA, and certainly to that of physicians and consumers- federal regulations put the burden upon drug manufacturers to warn of safety hazards associated with their drugs as these hazards come to light: "[T]he labeling shall be revised to include a warning **as soon as** there is reasonable evidence of an association of a serious hazard with a drug; **a causal relationship need not have been proved**." 21 C.F.R. § 201.57(e) [emphasis added]. The FDA considers it so important that a drug company warn of serious hazards associated with a drug as quickly as possible that it dispenses with

[5] *See, e.g.*, FDA MedWatch - December 2004 Safety-Related Drug Labeling Changes at http://www.fda.gov/medwatch/SAFETY/2004/dec.04_quickview.htm, Ex. 5. This document shows that warnings were added to no less than ten drugs during this reporting period.

the normal procedure of requiring FDA approval prior to a label change.[6] Instead, a drug company can "add or strengthen a contraindication, warning, precaution, or adverse reaction" for its drug at any time without prior FDA approval. 21 C.F.R. § 314.70(c)(6)(iii)(A).[7]

When 21 CFR § 201.57(e) was originally promulgated in 1979, the Commissioner of the FDA observed that "the act requires labeling to include warnings about both potential and verified hazards." 44 Fed. Reg. at 37,447 (June 26, 1979). App. at 137. He also emphasized that "these labeling requirements **do not prohibit** a manufacturer, packer, relabeler, or distributor from warning health care professionals whenever possibly harmful adverse effects associated with the use of the drug are discovered. The addition to labeling and advertising of additional warnings, as well as contraindications, adverse reactions, and precautions regarding the drugs, or the issuance of letters directed to health care professionals (*e.g.*, "Dear Doctor" letters containing such information) is **not prohibited by these regulations."** *Ibid.* [emphasis added].

C. An Overwhelming Majority of Courts have Confirmed the FDCA and the Associated Regulations Set Forth Minimum Safety Standards

Because the system of federal regulation of prescription drug labeling necessarily involves "labels [that] will evolve over time,"[8] and because the regulations confer on drug manufacturers the specific authority and duty to supplement drug labeling when appropriate, the overwhelming

---

[6] 50 Fed.Reg. 7452-01, 7470.

[7] "This particular regulation was promulgated precisely to allow drug-makers to quickly strengthen label warnings when evidence of new side effects are discovered. See 30 Fed.Reg. 993 (Jan. 30, 1965)." *Witczak v. Pfizer, Inc.*, 377 F.Supp.2d 726, 732 (D.Minn. 2005).

[8] *See Bates v. Dow Agrosciences, L.L.C.,* ___ U.S. ___, 125 S.Ct. 1788, 1802, 1792 (2005). In *Bates*, the U.S. Supreme Court reversed the Fifth Circuit's determination that the plaintiffs' claims were preempted by the express preemption clause of the Federal Insecticide, Fungicide, and Rodenticide Act ["FIFRA"], despite an amicus brief filed by the government in favor of preemption. Although FIFRA contains an express preemption clause – in contrast to the anti-preemption clause applicable in the case at bar – many of the general principles discussed in *Bates* apply.

majority of courts that have addressed the issue have held that FDA regulations set forth only minimum safety standards.[9] The latest RESTATEMENT OF TORTS, cited by the Supreme court in *Geier v. American Honda Motor Co.,* 529 U.S. 861, 869-70 (2000), also views safety standards such as those set forth in the FDCA as minimum rather than absolute. RESTATEMENT (THIRD) OF TORTS § 4(b) cmt. e (1998).[10] This recognition is important – and should be dispositive of Wyeth's motion – because if labeling requirements set forth only minimum standards, principles of conflict preemption do not bar failure to warn suits. *Geier*, 529 U.S. at 870.

IV. STATE COURT SUITS COMPLEMENT FEDERAL REGULATION RATHER THAN CONFLICT WITH IT

Products liability suits brought under state law serve an important role in federal regulation of prescription drugs. In industries in which labels "evolve over time," "tort suits can serve as a

---

[9] *E.g., Tobin v. Astra Pharm.*, 993 F.2d 528 (6th Cir. 1993); *Hill v. Searle Labs.*, 884 F.2d 1064, 1068 (8th Cir. 1989)("FDA regulations are generally minimum standards"); *Osburn v. Anchor Labs.*, 825 F.2d 908 (5th Cir. 1987) ("FDA regulations [] did not prevent [the manufacturer] from adding to its label warnings . . . "); *Wells v. Ortho Pharm. Corp.*, 788 F.2d 741, 746 (11th Cir. 1986) ("An FDA determination that a warning is not necessary may be sufficient for federal regulatory purposes but still not be sufficient for state tort law purposes."); *Brochu v. Ortho Pharm. Corp.,* 642 F.2d 652 (1st Cir.1981); *Salmon v. Parke Davis & Co.*, 520 F.2d 1359 (4th Cir.1975); *Cartwright v. Pfizer, Inc.,* 369 F.Supp.2d 876, 882 (E.D. Tex. 2005)("Numerous courts over the years have recognized that the FDCA and its associated regulations set out minimum requirements that drug manufacturers must follow which may be supplemented by state tort laws which are stronger."); *Witczak v. Pfizer, Inc.*, 377 F.Supp.2d 726, 732 (D.Minn. 2005)("Federal labeling laws are minimum standards; they do not necessarily shield manufacturers from state law liability."); *Motus v. Pfizer*, 127 F. Supp. 2d 1085 (C.D. Cal. 2000), *aff'd,* 358 F.3d 659 (9th Cir. 2004); *In Re Paxil Litigation*, 2002 WL 31375497 (C.D. Cal. 2002); *Ohler v. Purdue Pharm., L.P.*, 2002 WL 88945 (E.D. La. 2002)("FDA regulations appear to be minimum standards except in cases of express preemption."); *Eve v. Sandoz Pharm. Corp.*, 2002 WL181972 (S.D. Ind. 2002); *Caraker v. Sandoz Pharm. Corp.*, 172 F. Supp. 2d 1018 (S.D. Ill. 2001); *Globetti v. Sandoz Pharms. Corp.*, No. CV98-TMP-2649-5, 2001 WL 419160 (N.D. Ala. 2001); *Mazur v. Merck & Co.,* 742 F. Supp. 239, 247 (E.D. Pa.1990) ("[C]ompliance with an FDA regulation may establish that the manufacturer met the appropriate minimum standards of due care, but compliance does not necessarily absolve the manufacturer of all liability . . . ."); *Kociemba v. Searle & Co.,* 680 F. Supp. 1293, 1299 (D. Minn. 1988) ("FDA regulation of prescription drugs establishes minimum standards, both as to design and warning.") (citing *Graham v. Wyeth Labs.*, 666 F. Supp. 1483 (D. Kan.1987); *Stephens v. G.D. Searle*, 602 F. Supp. 379, 382 (E.D. Mich. 1985).

[10] "Subsection (b) reflects the traditional view that the standards set by most product safety statutes or regulations generally are only minimum standards. Thus, most product safety statutes or regulations establish a floor of safety below which product sellers fall only at their peril, but they leave open the question of whether a higher standard of product safety should be applied. This is the general rule, applicable in most cases."

catalyst" in the process of gathering information to push the evolution. *Bates,* 125 S.Ct. at 1802. A long history of tort litigation in an area strengthens the presumption against preemption, especially where preemption would deprive injured parties of a remedy. *Id*. at 1801. Where preemption would deprive consumers of a long-available form of compensation, therefore, the Supreme Court has ascribed preemptive intent to Congress only in the most compelling circumstances. *Id.* at 1801; *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 251 (1984)("It is difficult to believe that Congress would, without comment, remove all means of judicial recourse for those injured by illegal conduct."); *see also Sprietsma v. Mercury Marine*, 537 U.S. 51, 63 (2002) ("It would have been perfectly rational for Congress not to pre-empt common-law claims, which--unlike most administrative and legislative regulations--necessarily perform an important remedial role in compensating accident victims.").[11] The FDA itself has recognized "that product liability plays an important role in consumer protection." 59 Fed. Reg. 3944, 3948 (1994).

The FDCA provides no remedy to consumers injured by dangerous drugs. When Congress was considering legislation that ultimately was enacted as the Food, Drug, and Cosmetic Act of 1938, it specifically rejected a proposal to include a private right of action for damages because such a right of action already existed under state law. *See*, *e.g.*, Hearings Before Subcomm. of Comm. on Commerce on S. 1944, 73d Cong., 2d Sess. 400, 403 (1933); *see also* Adler & Mann, *Preemption and Medical Devices: The Courts Run Amok*, 59 Mo. L. Rev. 895, 924 & n. 130 (1995). Although Congress greatly expanded the regulatory role of the FDA in the 1962 Amendments, it provided no private cause of action for damages caused by unsafe drugs, again preserving the long-standing rights

[11] *Cf. Medtronic, Inc. v. Lohr,* 518 U.S. 470, 486-87 (1996)("Medtronic's construction of § 360k would therefore have the perverse effect of granting complete immunity from design defect liability to an entire industry that, in the judgment of Congress, needed more stringent regulation in order "to provide for the safety and effectiveness of medical devices intended for human use," 90 Stat. 539 (preamble to Act)).

of consumers to seek private redress under state law, except in the case of a "direct and positive conflict." Pub. L. No. 87-780, § 202, 1962 U.S.C.C.A.N at 909 (76 Stat. 779). Congress has amended the FDCA on many other occasions as well, but has never provided a remedy for injured consumers. Given the integral role that state tort suits play in the federal regulatory scheme, it is not surprising that, in the decades since the FDCA's enactment and up until 2002, no reported decision had held that the Act preempted a state-law damage action with respect to prescription drugs.

Far from avoiding a "positive and direct conflict," preempting lawsuits such as the ones at bar would actually thwart the primary purpose of the FDA:

> FDA's and [defendant]'s position vitiates, rather than advances, the FDCA's purpose of protecting the public. That is, FDA and [defendant] invite the Court to find that in enacting the FDCA for the purposes of protecting public health, Congress not only declined to provide for a private cause of action, but also eliminated the availability of common law state claims. This position contravenes common sense, *cf. Medtronic, Inc. v. Lohr*, 518 U.S. 470, 487 (1996), and the Court declines the invitation.

In Re Paxil Litigation, 2002 WL 31375497 at *1 (C.D. Ca. 2002).

V. THE SUMMARY JUDGMENT EVIDENCE IN LIGHT OF THE FEDERAL REGULATORY FRAMEWORK

When one understands that the FDCA and the accompanying regulations set forth only minimum safety standards in an industry where drug labeling is constantly evolving, and that the regulations place the duty on the manufacturers to add or strengthen their warnings when appropriate, the summary judgment evidence in this case is a "business-as-usual" portrait of the regulation of prescription drugs over the past few decades. In this regard, the summary judgment evidence does show that the FDA has occasionally considered a potential relationship between antidepressants and suicide. Until 2004, however, the FDA neither required nor prohibited a

warning of the association between Effexor and increased suicidality (and its precursors) for which Plaintiff advocates.[12] This refusal to require or prohibit a stronger warning brings this case squarely within the Supreme Court's unanimous decision in *Sprietsma,* 537 U.S. 51 (2002).

In *Sprietsma*, the Supreme Court considered whether the Coast Guard's decision not to require propeller guards on motor boats impliedly preempted a state-law damage action that alleged, among other things, that the manufacturer's motor boat was unreasonably dangerous because the motor was not protected by a propeller guard. Rejecting the manufacturer's preemption argument, the Court explained that "[i]t is quite wrong" to view a decision declining to impose a requirement as the "functional equivalent" of a prohibition against state regulation of the subject matter. Rather, a decision not to take regulatory action leaves the applicable law "exactly the same" as it was before the agency's consideration of the matter. *Id.* at 65; *accord Freightliner Corp. v. Myrick*, 514 U.S. 280, 289 (1995) (where an agency had no standard either requiring or prohibiting antilock brakes, state common law as applied to antilock brakes not preempted); *Puerto Rico Dept. of Consumer Affairs v. Isla Petroleum Corp*., 485 U.S. 495, 501, 503 (1988) (absent an explicit statement of intent, federal inaction has no preemptive effect). As the government explained, "the mere fact that the agency has made a considered decision to forego federal regulation does not, in and of itself, give rise to an inference that all state law on the subject—including state tort law—is meant to be

[12] As Plaintiff discusses in detail in the section entitled "The Nail in the Coffin" below, Wyeth itself gave a warning with respect to pediatric patients in August 2003, and the FDA did not prohibit it. This is the only actual evidence – as opposed to the hypothetical statements in the FDA's *Kallas amicus* – of an antidepressant manufacturer's giving a warning of the relationship between its drug and suicide that appears in the summary judgment record. Far from showing a "positive and direct conflict," this evidence shows that there is no conflict at all.

preempted." U.S. Br. 18, in *Sprietsma*, S. Ct. No. 01-706 (filed March 2002) (available at http://www.usdoj.gov/osg/briefs/2001/3mer/1ami/2001- 0706.mer.ami.html).[13]

As in *Sprietsma*, the FDA's decision not to request a suicide warning for Effexor prior to 2004 "does not convey an 'authoritative' message of a federal policy against" such a warning, *Sprietsma,* 537 U.S. at 67, and a jury verdict finding Wyeth liable for failure to warn would not conflict with any federal requirement.

VI. THE EVOLUTION OF ANTIDEPRESSANT LABELING CONCERNING SUICIDALITY

As Wyeth points out, the FDA has considered the relationship between antidepressants and suicide at various points in time. Nonetheless, Wyeth's implication that the FDA comprehensively analyzed the data prior to early 2004 is simply wrong. The FDA began to focus on this issue in the Fall of 2002. Prior to that time, it neither required nor prohibited warnings. Since that time, it has moved steadily towards more stringent warnings, directed to broader categories of patients.

During its review in Fall 2002 of a supplemental NDA submitted by GlaxoSmithKline ["GSK"] concerning studies of the use of Paxil by children, "FDA reviewers noted a greater number of adverse events coded under the term ' emotional lability' in the group of patients treated with Paxil compared to placebos in some, but not all, of the studies." App. 37 to Wyeth's Motion at 16. On October 10, 2002, the FDA requested that GSK reanalyze its pediatric data to help it understand the "greater number of adverse events." *Id*. at 16-17. The FDA received GSK's response, which

[13] Contrast *Sprietsma* with *Geier*; in which the Supreme Court found that the plaintiff's state-law claims seeking to hold Honda liable for not installing an air bag in her car would conflict with the agency's decision to give manufacturers a choice between air bags and other passive restraint systems. The Court found that the plaintiff's claims essentially forced the manufacturer to choose air bags, removing the choice that the agency had given it. In *Sprietsma*, the government explained that "*Geier* does not suggest that common-law suits will be preempted whenever the federal agency has focused its attention upon the particular aspect of motor vehicle performance that forms the basis of the plaintiff's claim." US Br. in *Sprietsma*, *supra*, at 19.

"suggested an increased risk (Paxil v. placebo) of various thoughts and behaviors coded as events considered 'possibly suicide related' and also for the subgroup of events that met [GlaxoSmithKline's] criteria for representing 'suicide attempts,'" on May 22, 2003. *Id*. at 17. On July 22, 2003, the FDA requested that Wyeth reanalyze its data concerning Effexor. *Id*. at 18 n.12. Wyeth sent out its "Dear Doctor" letter – which Plaintiff discusses at length below – on August 22, 2003.

In early 2004, the FDA convened an advisory committee to consider the association between antidepressants and suicidality. When the advisory committee convened on February 2, 2004, the Chairman noted:

> It is the controlled trial data that we believe is best able to help us provide an adequate answer to this question, but as you have heard, and you will hear throughout today's presentations, **we do not believe that this data until now has been provided to us in a way that would permit us to interpret it fully**.

Ex. 6 at 000087 [emphasis added]. *See also* Ex. 7 at 000004 and Ex. 8 at 000051. In an interview following the advisory committee's meeting, Dr. Russell Katz, the Director of the FDA's Division of Neuropharmacological Drug Products, explained further:

> [Y]ou know, it's common for us in other areas to ask companies to get specific data. We sort of, for certain things, we have a general way we do it. For instance, you know, trying to get data on certain side effects or whatever, is we say, you need to look for this thing in the following way, or you need to measure effectiveness in the following way. So there's more or less standard approaches to various things. **And there hasn't been one for suicidality to date.**

Ex. 9 at 000028 [emphasis added].

When the committee finally had the data in a form that allowed it to meaningfully consider the relationship among antidepressants, akathisia and suicidality, it saw clearly and acted quickly.

The committee recommended that the FDA immediately issue a warning about use of antidepressants by children and adolescents, a warning not only about suicide but also about signs that the drugs have caused "activation," *i.e.*, precursor conditions like agitation, akathisia, and confusion. Ex. 10 at 000007-9. On March 22, 2004, the FDA issued a Public Health Advisory, in which it asked the manufacturers of certain antidepressants to warn about a suicide risk for both children and adults. Ex. 11 at 000001. The FDA wrote that suicidality "might be the result of drug therapy" and asked that health care providers, patients, and their families be warned about the association between SSRIs and anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, and akathisia, among other things. *Id.*

On October 15, 2004, the FDA requested that manufacturers of antidepressants add a **BLACK BOX** warning to their respective labels, which included the statement: "A causal role for antidepressants in inducing suicidality has been established in pediatric patients."[14] The Request Letter appears at http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm, and is Ex. 13 to this Response. A "**BLACK BOX**" warning is second only to "**CONTRAINDICATIONS**" in terms of the "warning strength hierarchy" provided by FDA regulations. 21 C.F.R. § 201.57(e).

What happened after the October 15, 2004 Labeling Change Request Letter seems to have happened behind closed doors. The sworn testimony of the FDA's deputy director for the Office of New Drugs, Dr. Sandra Kweder, before the Senate Committee on Health, Education, Labor and Pensions regarding improving drug safety in the wake of the Vioxx debacle may offer the Court a glimpse of what transpired. When asked about the FDA's authority to require a drug company, to

[14] Wyeth's Dr. Joseph Camardo, whose testimony Plaintiff discusses at length below, was present at the September 14, 2004 session of the FDA Advisory Panel when Dr. Laughren, the top FDA official in the psychopharmacology area, stated that "causality has been established." Ex. 12 at 23-24; 314; 327-329.

change its label, Dr. Kweder testified that the FDA does not "have the authority to tell a company 'this is how your label has to look. This is the language that needs to go in your label, here's where it goes, end of story.' We have to negotiate with the company the specific language of how things should be worded, placement, those kinds of things. . . ." Ex.14 at 23. Wyeth's stance in the "negotiations" is clear from the testimony of one of its Senior VP's Joseph M. Mahady. In response to a question about how the "commercial impact" of a black box warning relates to Wyeth's decision to warn of safety hazards, Mr. Mahady answered: "To sacrifice a company's sales just to accept approval with a BLACK BOX is not a responsible action." Ex. 15.[15] The clear implication is there is a direct relationship between the severity of the warning and a drug company's sales, and that Wyeth is willing to compromise on safety to make more sales. Ultimately, the FDA approved a warning of an *association* between antidepressants and suicidality that omitted an assertion of *causality*. The black box warning as to pediatric patients, as well as the non-black box warnings as to adult patients, remained.

In May 2005, the FDA issued an Alert for Healthcare Professionals concerning the risk of "Suicidality in Pediatric Patients" on Effexor. Ex. 16. It actually demonstrates causality:

> "Increases in suicidal thinking or behavior due to drug can be expected in about 1 out of 50 treated pediatric patients."

Subsequently, on July 8, 2005, the FDA revised this Alert, broadening it to include "Suicidality in Pediatric and Adult Patients" and appears at http://www.fda.gov/cder/drug/InfoSheets/HCP/venlafaxineHCP.htm. Ex. 17. This Alert highlighted that:

[15] Ex.15 is both a DVD with a short video excerpt of this testimony as well as the transcript thereof.

> * "Several recent scientific publications report the possibility of an increased risk for suicidal behavior in adults who are being treated with antidepressant medications. Even before these reports became available, FDA began a complete review of all available data to determine whether there is an increased risk of suicidality (suicidal thinking or behavior) in adults being treated with any type of antidepressant medication. It is expected that this review will require a year or longer to complete. In the meantime, FDA is highlighting that adults being treated with any type of antidepressant medication, particularly those being treated for depression, should be watched closely for worsening of depression and for increased suicidal thinking or behavior."

VII. WYETH'S ILLUSORY CONFLICT

As shown above, Wyeth has had the power to add a warning of Effexor's association with suicidality, over and above the minimum standards set forth by the FDA, from the time of its initial approval by the FDA in 1993. It chose not to do so until August 2003 (and then only as to pediatric patients). Ex. 18. Once the FDA began to reanalyze the existing data using its "standard approach" in early 2004, however, it requested that Wyeth warn both as to pediatric and adult patients. The FDA confirmed this year that "[i]ncreases in suicidal thinking or behavior due to drug can be expected in about one out of 50 [Effexor] treated patients;" so there is clearly scientific support for an appropriate warning. *See* Ex. 17. Given this situation, what could possibly form the basis of a "direct and positive conflict" between the FDA's regulation of Effexor and Plaintiff's claims?

Wyeth has attempted to piggyback on Pfizer's motions with respect to Zoloft, and on two FDA amicus briefs submitted in Zoloft cases. As in those cases, there is a single asserted basis for conflict preemption: that giving a warning "was not, at the time, supported by the available scientific evidence," meaning that such a warning would be "false and misleading" and "would result in misbranding of the drug." Wyeth's Response at 19. This is a preposterous suggestion, for several reasons.

First, the sole conflict that Wyeth identifies has been confirmed to be no conflict at all. Wyeth bases its entire motion on *Dusek v. Pfizer, Inc.*: "[t]his is the same conflict identified by the *Dusek* court with respect to the Zoloft label." Wyeth's Motion at 22. The *Dusek* court found a conflict between a warning as to *causation*[16] and a provision in the "adverse reactions" section of the Zoloft label that provided that certain adverse reactions "were not necessarily caused by it." 2004 WL 2191804 at *6. As shown above, Wyeth now gives a stronger warning but the "not necessarily caused by it" language *remains on the label*. Ex. 20. Obviously, the FDA sees no conflict between this language and a warning of an association between Effexor and suicidality and its precursors.

Second, Wyeth and the other drug manufacturers possessed the evidence that led the FDA to add a warning in March 2004 for years. It was scientifically "available" all along if Wyeth had chosen to use it or to provide it to the FDA in the appropriate form.[17] It was only after the manufacturers "provided [the data] to us in a way that would permit us to interpret it fully," Ex. 6 at 000087, that the FDA analyzed it and finally requested the warning. There was no new data – only a reanalysis of data that Wyeth had for years. Surely a drug manufacturer with data in hand that justifies a warning, cannot simply sit back and wait for the FDA to act (or to request a reanalysis of existing data), confident that it can avoid its duty to comply with 21 C.F.R. § 201.57(e) and 21 C.F.R. § 314.70(c)(6)(iii)(A) by shouting "preemption: the FDA had not made us warn yet."

---

[16] The plaintiffs' failure to warn claim in *Dusek* was limited to a warning of causation. Plaintiff's claims in this case encompass a warning of association, as discussed more fully below. *See* Complaint at 4-5, ¶10, Ex. 19.

[17] If the Court chooses to follow Wyeth's suggestion that it consider evidence of other antidepressants, Plaintiff also emphasizes the finding of the federal district court in Wyoming that "The Jury's Verdict was Supported by Reliable Scientific Evidence" in a Paxil "failure to warn" case tried in the summer of 2001. *Tobin v. SmithKline Beecham Pharms.*, 164 F.Supp.2d 1278, 1283 (D.Wy. 2001).

> To argue that, once the FDA approves a package insert, the defendant has no further duty to give an adequate warning creates an incentive for pharmaceutical companies to oppose all efforts by the FDA to secure clearer package inserts. If that were the case, drug manufacturers could avoid liability simply by resting on the formerly approved package insert (regardless of how long ago the approval occurred and how much information about the drug had changed) and resist all efforts to change it.

Globetti v. Sandoz Pharm. Corp., 2001 WL 419160 at 2 n.1 (N.D. Ala. 2001).

Third, the repetition of the mantra, "FDA's judgment," in the amicus brief in *Kallas, e.g., Amicus* Ex. 21 at 26, cannot generate a "positive and direct conflict." The "FDA's judgment" is relevant to the extent that the FDA is empowered to file suit against a drug manufacturer for misbranding if its labeling is "false or misleading in any particular or does not provide adequate warnings against any use dangerous to health." 21 U.S.C. § 352(a), (f) and (j); 21 U.S.C. § 321(n); Amicus at 6. *Id*. The FDA is not, however, empowered to make a determination of misbranding. As Chief Judge Rosenbaum of the Minnesota district court wrote on July 20, 2005:

> Furthermore, even if the Court credited the *Motus* brief as an attempt by the FDA to articulate an official agency position, it would still fail to preempt plaintiff's claim. This is because the FDA has no authority to declare, *ipse dixit*, that a label is false and misleading. Rather, the government must initiate an enforcement action to establish that the drug is in fact misbranded. See 21 U.S.C. §§ 331-37, 352.

Witczak v. Pfizer, Inc., 377 F.Supp.2d 726, 730 (D. Minn. 2005). Ultimately, whether a drug is in fact misbranded will be determined by a jury, after a trial. *See Bates,* 125 S.Ct. at 1803. There could be a "positive and direct conflict" only if the FDA initated a suit for misbranding and prevailed. Given the FDA's actions since 2002, even if the FDA had initiated an action for misbranding against Wyeth, it would have lost miserably.

Fourth, it is extremely difficult to believe that the FDA would have considered a warning by Wyeth of the association between Effexor and increased suicidality in January 2002 "false and misleading" so as to justify a misbranding action in the first place. There is no assertion in the government's brief in *Kallas* that the FDA would have actually initiated such an action.[18] Dr. Joseph Camardo, Wyeth's Senior VP and designated public spokesman on this very issue, has testified that the FDA has never threatened Wyeth, much less sued it, for misbranding Effexor, Ex. 22. Judge Steger's comments bear repeating once again to illustrate this point: "Given the hearings by both Congress and the FDA regarding suicidality, the FDA's PDAC's recent decision to recommend black box warnings regarding suicidality in children and adolescents, and the numerous experts who have concluded that there is a link between SSRIs, like Zoloft, and suicidality, it would be **inconceivable** to this Court to argue that an additional warning regarding suicidality would be false or misleading." *Cartwright* 369 F.Supp.2d at 885-86 (E.D. Tex. 2005)[emphasis added].

Fifth, it is interesting that Wyeth now attempts to piggyback on the preemption efforts of Pfizer, an SSRI drug. Pfizer has been increasingly unsuccessful in these motions as the FDA's actions have made it increasingly clear there is no conflict, losing its argument in seven cases, and winning it on analogous facts in only one.[19] Additionally, Wyeth has taken pains to confirm that it

---

[18] The government's brief in *Kallas* loses any credibility it might otherwise have when the government suggests that the FDA would have considered any warning "false and misleading" with respect to Shyra Kallas, who was 15 years old when she was prescribed Zoloft for warts. Her initial prescription was on October 8, 2002. Two days later, the FDA requested that GSK reanalyze its pediatric data to help it understand the "greater number of adverse events" it had observed. Amicus at 16-17. The government's position in the amicus brief that it would have considered a warning to a 15-year old girl's physician "false and misleading" when that prescription occurred at the same time that the FDA was requesting that GSK explain a "greater number of adverse events" in its pediatric and adolescent data is unpersuasive, to say the least. As the Supreme Court explained in *U.S. v. Mead*, 533 U.S. 218, 228 (2001), the deference that courts give to the positions of federal agencies varies, extending "from great respect at one end" to "near indifference at the other." Interpretations advanced for the first time in a litigation brief reside at the "near indifference" end of the spectrum."

[19] As Plaintiff explains below, *Dusek,* does not support Wyeth's position, and the *Dusek* court would have denied preemption on the facts of this case.

is not an SSRI drug like Zoloft for regulatory purposes. In the summer of 2003, in anticipation of its forthcoming pediatric suicidality precaution, Wyeth emailed the FDA and asked it to agree with Wyeth that "venlafaxine is a non-SSRI." When the FDA failed to respond in a timely fashion, Wyeth sent reminder emails. Ultimately, on October 23, 2003, the FDA concurred, " . . . we agree that venlafaxine is a non-SSRI." Ex. 23.

Finally, it is ironic that Wyeth – the only antidepressant manufacturer which even arguably attempted to discharge its duties under 21 C.F.R. § 201.57(e) and 21 C.F.R. § 314.70(c)(6)(iii)(A) with respect to the suicidality issue – would now claim preemption, necessarily claiming that its own actions constituted misbranding. Plaintiff elaborates on this irony next.

VIII. THE NAIL IN THE COFFIN

Plaintiff returns to the bedrock principle that "a hypothetical or potential conflict is insufficient to warrant the preemption of" a state law, *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982). This is important because there is only one piece of evidence in the summary judgment record in which an antidepressant drug manufacturer actually added a warning of increased suicidality prior to the FDA's requesting it to do so. This is the only evidence of an actual warning, as opposed to a hypothetical warning. On August 22, 2003, Wyeth sent out a "Dear Doctor" letter in which it unilaterally, without prior FDA approval, warned of hostility and suicidality for pediatric patients taking Effexor XR. *See* Ex. 18, *supra*. The FDA allowed this warning to stand for seven months until it requested that Wyeth (and other antidepressant manufacturers) issue an even *stronger* warning.

Realizing that its own [appropriate] use of 21 C.F.R. § 201.57(e) clearly demonstrates that it is entirely possible to comply with both federal regulations and state failure to warn standards,

Wyeth must now advocate that the FDA somehow disallowed its August 2003 "Dear Doctor" letter. *See, e.g.,* Wyeth's Motion at 15 ("the FDA instructed Wyeth to remove its pediatric statement . . . "). Its whispered sophistry in the judicial ear is, "Your Honor, we tried to warn, but the FDA wouldn't let us." The evidence is to the contrary.

A. FDA Officials Acknowledge Wyeth's Authority to Unilaterally Add a Warning and to Send the 8/22/03 "Dear Doctor" Letter

In a January 2004 Memo, the FDA's Dr. Thomas Laughren emphasized that Wyeth's action was specifically permitted: "[i]t should be noted that sponsors have the authority to make changes of this nature, *i.e.*, that are perceived to strengthen labeling from the standpoint of safety, without prior approval by FDA." Memorandum - Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, January 5, 2004, *See* Ex. 8, *supra* at 000050-51, 59-60. FDA's Director of the Office of Drug Evaluation, Dr. Robert Temple agreed: "Typically, those are done in association with actual labeling changes. But they needn't be, and of course, we will contemplate making labeling changes." Transcript of Post-PDAC interview with Drs. Russell Katz and Robert Temple of the FDA, February 2, 2004, Bethesda, Maryland, *see* Ex. 9 *supra* at 000032033. In his September 2004 congressional testimony, Dr. Temple made it even clearer:

> Ms. DeGETTE: Well, let me ask you this. In the spring or summer of 2003, Wyeth came to the FDA, and they wanted on their own – we heard this in the last hearing – to strengthen warnings on Efexir [sic], and the FDA asked them not to do that. Is that right?
>
> Dr. TEMPLE: Not quite. **They were allowed to do that**, and **they did it until we created a new stronger warning** or – you can call it strong or not – a different warning **in the warning section**. It prominently said you really need to watch patients, and we thought that was a more trenchant warning. That was in response to the Advisory Committee.

Ex. 24. *Hearing before the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce,* House of Representatives (September 23, 2004), Serial No. 108-125, at p. 75.

B. Wyeth Admits There was no Misbranding Action

In his deposition on November 2, 2005, Wyeth's Senior VP and signer of a subsequent "Dear Doctor" letter, Dr. Joseph Camardo, attempted to bolster Wyeth's asserted conflict by volunteering that the FDA "revoked" the "warning" and that Wyeth was under threat of "misbranding" as a result of its August 2003 "Dear Doctor" letter. Ex. 22 *supra* at 50-52, 104. The contentions did not survive cross examination.

Dr. Camardo had to first admit that the word "misbranding" was used neither by him in this context nor, to his knowledge, by anyone else at Wyeth or in any Wyeth document -- until he was prepped by counsel for the deposition. In short, it was quite obviously a word which was implanted into his consciousness in the pre-deposition woodshed. He also admitted that he was unaware of the FDA's threatening Wyeth with a misbranding action over the Effexor/suicide label change. *Id.* at 52, 93-94.

With regard to the contention that the FDA "revoked" the wording, Dr. Camardo confessed that Wyeth did absolutely nothing to change the label between August 22, 2003, and March 22, 2004, when it was asked by the FDA to join the rest of the antidepressant industry by adopting *more* stringent, class-wide warnings.[20] *See* Ex. 11, *supra*.

[20] The documentary record supports Dr. Camardo's clarified testimony. Prior to Wyeth's issuing its "Dear Doctor" letter on August 22, 2003, there were at least seven email or telephone contacts between Wyeth and the FDA concerning the pending label change. These appear as Ex. 25, and are summarized in Ex. 26. Between August 22, 2003 and the Public Health Advisory on March 22, 2004, there were at least 30 email, telephonic, and/or written communications between Wyeth and the FDA. These appear as Ex. 27 and are summarized in Ex. 28.

To understand why the March 2004 warning was actually stronger than the August 2003 "Dear Doctor" letter, the Court should understand that there is a FDA-prescribed hierarchy of cautionary statements regarding risks associated with drugs. Contraindications are at the top; followed by **BLACK BOXED WARNINGS;** then regular Warnings; then Precautions. *Id*. at 99, 103. *See also* 21 CFR §§ 201.56-.58. Ex. 22. Dr. Camardo conceded that: (1) Although the August 22, 2003, suicide risk language was contained in the "Precautions" section, the March 22, 2004, change (which was actually implemented by Wyeth via a second "Dear Doctor" letter signed by Dr. Camardo himself on June 4, 2004) moved it up the ladder to the "Warnings" section. *Id.* at 104, 249; (2) While the August 2003 precaution alerted physicians to a risk of hostility and suicidality only with regard to pediatric patients, the new Warning extended to **adults** as well. *Id*. at 107, 249; and (3) While the August 2003 precaution focused only on physicians, the March 2004 Warning addressed the need to alert patients, their families, and caregivers as well, and was posted on the FDA's website in the form of a Public Health Advisory. *Id*. at 107-08, 249; Ex. 22 *supra*.

The March 2004 warning contained the following language:

> **Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to discontinuing the medication in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

A fair reading of these exhibits reveals that: (1) the FDA did not question Wyeth's right and duty to add a warning; (2) the FDA did not ask to "pre-clear" the "Dear Doctor" letter or give a time frame in which it would review Wyeth's language; (3) while there was discussion as to the wording and placement of Wyeth's warning, there was no attempt by the FDA to "revoke" the warning; and (4) the FDA's primary concern was not Wyeth's added warning, but the receipt of its reanalyzed pediatric data.

See Ex. 11 *supra*. Faced with these facts, Dr. Camardo retrenched considerably on his "revoked" description of the FDA's action: "I think the later [March '04 FDA] warning is substantially more elaborate and somewhat more prominent . . . " Ex. 22 *supra* at p. 252.

With no evidence that the FDA "revoked" or "disallowed" its added warning about suicidality in August 2003, Wyeth is left with its own action as the best evidence that there is no "positive and direct conflict" between Plaintiff's claims and federal regulation of Effexor. As Wyeth itself has demonstrated, it is far from impossible to comply with both the minimum safety standards imposed by federal law and the "adequate warning" standards imposed by Texas law.

IX. WYETH CANNOT RIDE ON PFIZER'S SHABBY COATTAILS

Wyeth attempts to ride Pfizer's coattails on the two cases that Pfizer actually won, ignoring that one of the two does not support its motion at all, and failing to address that Pfizer has lost seven others, including every case decided this year (two of which include denials of Pfizer's motions for reconsideration based on the government's brief in *Kallas*) and the only one in this District.

A. Scorecard of Pfizer's Preemption Case

Nine trial courts (eight federal district courts and one state court) have now ruled on Pfizer's claims of preemption concerning Zoloft-induced suicidality. Seven have denied the claim outright. *Motus v. Pfizer, Inc.*, 127 F. Supp. 2d 1085, 1099-1100 (C.D. Cal. 2000), *aff'd,* 358 F.3d 659 (9th Cir. 2004)(Ninth Circuit did not address preemption), Ex. 29; *Cloud v. Pfizer, Inc.,* Civil Action No. CV 99-627-TUC-WDB (D.Ariz. 2001), Ex. 30; *Miles v. Pfizer, Inc.,* Civil Action No. 03-731-C (M.D. La. March 30, 2005), Ex. 31; *Cartwright v. Pfizer, Inc.,* 369 F.Supp.2d 876, 882 (E.D. Tex. 2005), Ex. 32; *Zikis v. Pfizer, Inc*., 2005 WL 1126909 (N.D.Ill. 2005), Ex. 33; *Witczak v. Pfizer, Inc.*, 377

F.Supp.2d 726, 732 (D.Minn. 2005), Ex. 34; and *Szybinski v. Pfizer, Inc*., Cause No. YC047439 in the Superior Court of California, County of Los Angeles, Ex. 35.

Dusek deserves special mention because the court would have denied preemption in that case but for a stipulation– that has been made in none of the other cases – that rendered the facts before the court "unique." *Dusek v. Pfizer, Inc*., No. H-02-3559, 2004 WL 2191804 at *1 (S.D. Tex. Feb. 20, 2004). The plaintiffs' counsel in that case entered into a stipulation that he believed would narrow the issues for discovery so that the court could determine the preemption issue early. The stipulation provided: "Pfizer's failure to warn that Zoloft can and does cause suicide in some patients proximately caused Decedent's ingestion of Zoloft and thereby proximately caused him to commit suicide." *Ibid*. The district court considered this stipulation an amendment of the plaintiffs' pleadings, and limited their failure to warn claim to one asserting a failure to warn of a causal relationship between Zoloft and suicide, rather than a failure to warn of an association. After limiting its analysis to a failure to warn of a causal relationship, the court recognized "a difficult and very close question of conflict preemption," *Id*. at *3; but ultimately found that a causal warning would conflict with another provision in the "adverse reactions" section of the Zoloft label that provided that suicidal activities "were not necessarily caused" by Zoloft. Id. at *6. Importantly, the court wrote that:

> If Plaintiffs were advocating for a warning that simply stated that there was an association between Zoloft and suicide, or another warning that did not attest to the existence of a causal relationship, the change could be implemented prior to FDA approval, because a conflict would not exist.

Id. at *9. To shoehorn Plaintiff's failure to warn case in this case into the *Dusek* mold, Wyeth has had to attempt to limit her claim to one for a causal warning. *E.g.*, Wyeth's Motion at 22. Its effort

must fail. Plaintiff's pleading clearly encompasses a warning of an association as opposed to one of causation. *E.g.*, Complaint at 4-5, ¶10[21] It is clear that the *Dusek* court would have refused to find preemption on the facts of this case.

That leaves *Needleman* as the lone case that even arguably supports Wyeth. Frankly, this now-settled case is an aberration. The court erred from the start by noting that "[t]his case is quite similar to *Dusek,"* 2004 WL 1773697 at *5, despite the *Dusek* court's emphasis that its holding rested entirely on a stipulation of a causal warning that did not exist in *Needleman*. Given the unanimity of the preemption decisions subsequent to *Needleman*, including Judge Steger's observation that "it would be inconceivable to this Court to argue that an additional warning regarding suicidality would be false or misleading," 369 F.Supp.2d at 886; Congress' anti-preemption statement in 76 Stat. 779, which the court does not even cite; the FDA regulations discussed *supra*; and the FDA's activities in 2004-05, most of which were not before the court, Plaintiff asserts that this court should give the *Needleman* opinion no weight.

The current status of these nine cases is also of interest. *Motus* and *Cloud* ended with summary judgments on non-preemption grounds. *Dusek, Needleman, Miles*, and *Cartwright* have been settled (as has *Kallas*, the case in which the government submitted its 2005 *amicus* brief). *Szybinski* is on appeal to the California court of appeals. Pfizer moved for reconsideration of both *Zikis* and *Witczak* in light of the amicus brief in *Kallas*. The *Witczak* court summarily denied Pfizer's motion on September 23, 2005. Ex. 34. On November 8, 2005, the *Zikis* court denied

[21] ("On March 22, 2004, the FDA itself finally realized that the **association** between these serotonergic medications and suicidality was important enough to merit a warning. It issued a "Public Health Advisory" in which it "recommended," among other things, that Wyeth issue a warning about this **association**. Wyeth has now complied with this recommendation. Unfortunately, however, this warning was "too little/too late" for the Ackermann family.")[emphasis added], Ex. 11 *supra*.

Pfizer's motion, issuing a concise opinion explaining why the FDA's brief makes no difference vis-a-vis the preemption issue. *Zikis v. Pfizer, Inc.*, 2005 WL 3019409 (N.D.Ill. 2005), Ex. 33.

B. Substantial Evidence Indicates Effexor is More Dangerous Than Zoloft

Another reason which militates quite heavily against Wyeth's attempt to ride coattail on Pfizer is the fact that Effexor is, by several objective indicia, substantially more dangerous, from a hostility/suicidality standpoint, than Zoloft. Three examples will suffice to illustrate the point. First, although Pfizer has repeatedly pounded the table to declare that no person actually committed suicide[22] during the Zoloft clinical trials, the same cannot be said to be true of Effexor. The Effexor label, and Dr. Camardo's testimony, both frankly concede that there were seven actual completed suicides by patients taking Effexor or Effexor XR in Wyeth's clinical trials, and 36 suicide attempts. Plaintiff has alleged, on information and belief, that Wyeth's clinical investigators, and/or Wyeth itself, have made "causality assessments" with respect to one or more of these incidents in which they decided that the suicidality was either "definitely" or "probably" related to the drug.[23] But, regardless of whether or not Wyeth itself has ascribed causality in these circumstances to the drug, its own clinical trial data is extremely damning. Specifically, the data submitted by Wyeth to the FDA shows that in these "pivotal" trials, 3082 patients were treated with venlafaxine vs. 739 patients on placebo. Seven of the Effexor patients completed suicide, and 36 made a suicide attempt. Thus, the percentage of patients who either attempted or completed suicide was 1.40%. The comparable

---

[22] Ironically, Wyeth did the same thing in its August 22nd "Dear Doctor" letter and in Dr. Camardo's September 2004 testimony before the FDA panels, *i.e.*, it took pains to point out that "Thankfully, no child committed suicide in any of these studies", but failed to point out that there were seven completed suicides in its adult clinical trials.

[23] In his November 2, 2005, deposition, Dr. Camardo admitted that such causality assessments are routinely done, and further admitted that the information concerning them could easily be retrieved from Wyeth's clinical trial databases. Plaintiff has asked that information be provided in sufficient time to be included as an exhibit to this Response. Because Wyeth was not forthcoming, counsel has prepared a Rule 56(f) affidavit. Ex. 38.

percentage of placebo patients is 0.41%. In scientific jargon, this translates to a relative risk of a suicidal act, lethal or not, of 3.43 to 1, with a 95% confidence interval of 1.07 to 11.02 and a p value of .027. This is hard, data-based evidence of a serious problem. Ex. 36 is the report of Plaintiff's expert in this case, Dr. David Healy, concerning the significance of this and other evidence of a causal relationship between Effexor and suicidality.

Secondly, according to a FDA-mandated "reclassification" of suicidality by experts at Columbia University, the "relative risk" of suicidality for patients taking Effexor is approximately four times higher than that for patients taking Zoloft. Ex. 37 is page 27/130 of the FDA Document. Table 10, contained therein, demonstrates that the relative risk for Effexor (venlafaxine) is 8.84, as compared to 2.16 for Zoloft. Although he initially tried to explain these numbers away, eventually, in his deposition, Dr. Camardo had to concede that the fact that Effexor was the only drug for which the "confidence interval" (CI) did not include the integer "1," meant that the data concerning this drug were more reliable, and had a lower potential "rate of error," than the data concerning Zoloft and the other SSRI drugs.

Third, another government-sanctioned barometer of danger is the UK's "Toxicity Index." There again, the number for Wyeth's Effexor, *i.e.*, 13.2%, is much higher than that for Zoloft, *i.e.*, 1.2% – indeed, it is higher than all of the SSRI's combined.[24] Ex. 39.

Finally, it should be reiterated that, from a regulatory standpoint, Wyeth sought to distance itself from the other SSRI's on the suicidality issue. As mentioned earlier, in the summer of 2003, and previous to the forthcoming PDAC and subsequent warnings, Wyeth repeatedly emailed the

[24] Wyeth has an explanation for virtually everything damning. Therefore, it will come as no surprise to counsel or the Court, but should nevertheless be acknowledged, that Wyeth has challenged the British government's findings. Ex. 22 at 209-11.

FDA regarding the FDA's view of Effexor and its status as a Non-SSRI. Ultimately, the FDA concurred with Wyeth's beliefs that Effexor is not an SSRI, " . . . we agree that venlafaxine is a non-SSRI." Ex. 23. It is clear that Wyeth sought to distance itself from the other SSRI's in order to maximize its' market position; it is only now that it seeks to scamper back under the umbrella of the SSRI label for "preemption" protection.

X. CONCLUSION

Wyeth sought from inception to delay this case so that it could pursue a preemption defense. It is time for the delay to stop. For the foregoing reasons, Wyeth's ill-founded motion should be denied.

//
//
//
//
//
//
//
//
//
//
//
//
//
//
//
//
//
//
//
//
//
//
//
//
//

Respectfully submitted,

VICKERY & WALDNER, LLP

/s/

Andy Vickery
Texas State Bar No. 20571800
One Riverway Drive, Suite 1150
Houston, Texas 77056-1920
Telephone: 713-526-1100
Facsimile: 713-523-5939
Email: *andy@justiceseekers.com*

Certificate of Service

I hereby certify that on November 23, 2005, I electronically transmitted the foregoing document to the Clerk of Court using the ECF System for filing and transmittal of a Notice of Electronic Filing to the following ECF registrants:

Michael R. Klatt
Kelly R. Kimbrough
CLARK, THOMAS & WINTERS
P. O. Box 1148
Austin, TX 78767-1148

Terence Murphy
Kelly Stewart
JONES DAY
2727 North Harwood Street
Dallas, TX 75201

Mark Hermann
Edward Sebold
JONES DAY
North Point
901 Lakeside Avenue
Cleveland, OH 44114-1190

/s/
Andy Vickery